CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ARTHRITIS DRUGS ADVISORY COMMITTEE MEETING

DATE OF MEETING: 12/1/98

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AGENDA

Arthritis Advisory Committee
Food and Drug Administration
Center for Drug Evaluation and Research

Town Center Hotel, 8727 Colesville Road, Silver Spring, MD

December 1, 1998
NDA 20-998, Celebrex™ (celecoxib) Searle

Agenda

8:00 Call to Order, Introductions: Steven Abramson, M.D.,
Acting Chair, Arthritis Advisory Committee
Meeting Statement: Kathleen Reedy, Executive Secretary
Arthritis Advisory Committee
Introductory Comments: Robert DeLap, M.D., Director, ODEV
John Hyde, M.D., Acting Deputy Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs

8:30 Searle Presentation
Introduction: Dr. P.Needleman, Ph.D., Co-President Searle
Chief Scientist Monsanto
Non-clinical Overview: Dr. P. Isakson, Ph.D.
Executive Director and Senior Fellow COX-2 Technology
Clinical PK: Dr. A. Karim, Ph.D., ABCP Distinguished Scientist,
Senior Director, Clinical Pharmacokinetics and Bioavailability
Clinical: Dr. G. Steven Geis, Ph.D., M.D, Vice President
Celecoxib Clinical Development

10:00 Break

10:15 FDA Presentation
Introduction, Osteoarthritis, Rheumatoid Arthritis:
James Witter, M.D., Ph.D., Medical Officer,
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs
Pain: Mordechai Averbuch, M.D., Medical Officer,
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs
Renal: Douglas C. Throckmorton, M.D., Medical Officer,
Division of Cardio Renal Drug Products
GI: Lawrence Goldkind, M.D., Medical Officer,
Division of Gastro-Intestinal and Coagulation Drug Products
Pharmacology/Toxicology: Josie Yang, Ph.D.,
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs
PharmacoKinetics: Sue-Chih Lee, Ph.D.,
Office of Clinical Pharmacology and Biopharmaceutics
Conclusion: James Witter, M.D., Ph.D., Medical Officer,
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs

11:15 Open Public Hearing
12:15 Lunch
1:30 Discussion and Questions
3:00 Break
5:00 Adjourn

ARTHRITIS ADVISORY COMMITTEE
CENTER FOR DRUG EVALUATION AND RESEARCH

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Arthritis Advisory Committee

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Guest Experts, Non Voting

Denis M. McCarthy, M.D.
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Chief, Division of Gastroenterology
University of New Mexico Medical School
Chief, Gastroenterology and Hepatology
New Mexico Regional Federal Medical Center
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Earl D. Silverman, M.D., FRCPC
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Open Public Hearing

1. **SmithKline Beecham Pharmaceuticals:**
   Robert H. Palmer, M.D., Group Director-Rheumatology
   Clinical Reserch and Development

2. **Whitehall-Robins:**
   Stephen A. Cooper, DMD, PhD, Vice President
   Clinical and Medical Affairs

3. **Nonprescription Drugs Manufacturing Association:**
   William Soller, Senior Vice President

4. **Bayer Corporation:**
   letter

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QUESTIONS

Arthritis Advisory Committee

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Questions

Efficacy

1. Should celecoxib be approved for the indications of the treatment of the signs and symptoms of OA and RA?

2. For the Indication "Management of Acute Pain", the Division's usual requirement is replicated evidence of efficacy in at least two different types of pain models. Traditionally, one type should be a single-dose model (e.g. dental pain) while the other type should be a multiple-dose model (e.g. post-operative, dysmenorrhea, etc.) studying patients with short-term (usually several days) therapy. While the replicated dental pain studies in this NDA support the analgesic efficacy of celecoxib, the multiple-dose studies are inconclusive (failed studies). The trials in OA are felt to be only supportive of the analgesic acute efficacy of celecoxib. The Agency believes that additional data are needed to support the acute pain indication. Does the committee agree? If so, what additional evidence should be provided?

Gastrointestinal

3. At prior AAC meetings on this subject, endoscopic studies have been viewed as surrogates of clinically meaningful endpoints. Given that celecoxib, in these endoscopic studies, has demonstrated consistent statistical superiority to only two of the three NSAIDs studied, what comparisons (if any) should be allowed in the labeling between celecoxib and these NSAIDs? Can these data be extrapolated to make comparisons between celecoxib and all other NSAIDs as well?

4. An underlying concept of the celecoxib development program has been that COX-2 selectivity would provide enhanced GI safety. While the celecoxib studies completed to date suggest that endoscopically diagnosed ulcers may occur less frequently with celecoxib treatment compared to NSAID comparators, studies completed to date have not included definitive comparisons of clinically significant GI adverse events. Is the NSAID warning template still appropriate, pending completion of appropriately powered trials to assess the incidence of significant GI events with celecoxib compared to one or more NSAID products? Or should qualifications be made to the NSAID GI warning template, while noting the limited experience with the new molecular entity?

5. NSAID labeling currently recommends against concurrent use of aspirin and NSAIDs. In view of the apparent lack of antiplatelet effect and the limited data from controlled endoscopy studies, what recommendations, if any, should be made concerning use of prophylactic low dose aspirin concurrently with celecoxib?

Renal

6. **The sponsor and the FDA have agreed that the overall renal effects of celecoxib, including the incidence of peripheral edema and other renal adverse effects, are similar to those of currently approved NSAIDs.**

a. Do you agree with this assessment?

b. How should any conclusion be reflected in labeling?

7. The NDA did not collect data on serum bicarbonates. Given the other laboratory abnormalities noted in the NDA:

a. Should additional safety studies be required?

b. How should this absence be reflected in labeling?

Other Issues

8. Information obtained from pharmacokinetic studies indicates that elderly subjects have a 40% increase in Cmax and a 70% increase in AUC. The FDA proposed label calls for initiating therapy with the lowest dose and titrating up slowly. Does the committee agree?

9. Celecoxib is almost entirely dependent upon hepatic metabolism (via P450 2C9). In patients with mild or moderate hepatic insufficiency should the dose or dosage regimen be altered?

Mild hepatic insufficiency (plasma celecoxib levels 1.3-1.4x normal)

Moderate hepatic impairment (plasma celecoxib levels > 2x normal)

10. At the present time there are no studies in subjects with severe hepatic failure. Should the sponsor be required to do studies which monitor both pharmacokinetics and clinical outcome (i.e. adverse events) prior to making labeling recommendations for this patient population?

11. Please provide recommendations for any Phase 4 studies for **Celebrex™** .